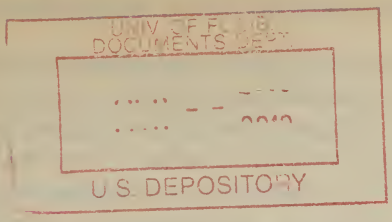
A 7.4:73



Issued June 24, 1911.

United States Department of Agriculture,

BUREAU OF CHEMISTRY—Circular No. 73.

H. W. WILEY, Chief of Bureau.

A CHEMICAL INVESTIGATION OF THE OIL OF CHENOPODIUM.

By E. K. Nelson,

Assistant Chemist, Division of Drugs.

INTRODUCTION.

American wormseed oil, official in the United States Pharmacopœia as *Oleum chenopodii,* is distilled from *Chenopodium ambrosioides,* var. *Anthelmintica.* It is used as a remedy for worms, particularly for Ascarides, which it seems to narcotize so that they can be eliminated by means of a laxative. The larger part of this oil produced in the United States is distilled from an herb grown in a section of Carroll County, Md., and is known in the trade as "Baltimore" wormseed oil.

The chemistry of oil of chenopodium has, until recently, been but little investigated. The first recorded examination of this oil was undertaken by Garrigues,[1] in 1854, who reported the presence of two constituents, one of which he described as a hydrocarbon boiling at 176° C., and the other as a liquid of the formula $C_{10}H_{16}O$.

Kremers [2] examined chenopodium oil in 1907, from the results of which examination he suspected the presence of a most unstable alcohol. Schimmel & Co.,[3] in 1908, reported an extensive investigation of the oil. By fractionating at reduced pressure (the oil explodes on attempting to distil it at atmospheric pressure) they separated a liquid substance, designated by them ascaridol, which constitutes the major portion of the oil, and to which its peculiar chemical as well as medicinal properties seem to be due. Ascaridol afforded on analysis the formula $C_{10}H_{16}O_2$. It is described as a yellow oil possessing a peculiar, repulsive odor suggesting both camphor and

[1] Amer. J. Pharm., 1854, 26:405. [2] Pharm. Rev., 1907, 25:155. [3] Report, April, 1908.

carvone. Toward reagents which would characterize it as an alcohol, an aldehyde, a ketone, or a phenol, ascaridol was found to be absolutely indifferent. Many attempts were made to ascertain the chemical nature of this substance, without results. They found that on heating ascaridol to 150° C. a molecular rearrangement apparently took place, and that the product of conversion, on combustion, gave values which agreed fairly well with the formula $C_{10}H_{16}O_2$. Ascaridol, when allowed to drop into concentrated sulphuric acid, or when reduced with zinc dust and acetic acid, formed cymene. No cymene was formed from the conversion product, either on treatment with zinc dust and acetic acid or with formic acid.

Besides cymene, Schimmel & Co. found a ketone, probably carvenone, to be formed on reducing ascaridol with zinc dust and acetic acid. The lighter boiling fraction of the oil was found to consist mainly of cymene, mixed, as the optical activity would indicate, with a terpene.

EXAMINATION OF AUTHENTIC SAMPLES.

In October, 1910, authentic samples of chenopodium oil were collected by the writer in the producing section of Maryland for the purpose of making a chemical examination as well as to determine the physical variations. Three samples were collected from a large steam still representing three different crops of the herb. A fourth sample was collected from one of the old-fashioned "pot" stills. The following are the results of a physical examination of these samples:

Physical tests on four authentic samples of chenopodium oil.

Determinations.	Steamed distilled samples.			Pot-distilled samples.
	No. 1	No. 2	No. 3	No. 4
Specific gravity $\left\{\frac{25° \text{ C.}}{25° \text{ C.}}\right\}$	0.9691	0.970	0.955	0.9584
n_D at 25° C.	1.4726	1.4723	1.4726	1.4725
α_D at 25° C.	−5.4°	−6.2°	−8.8°	−6.3°
Solubility in 70 per cent alcohol	1:3	1:3	1:7	1:6

For a preliminary chemical examination of chenopodium oil a sample was purchased on the market prior to the distillation of the fall crop. This sample, which must have been at least a year old, afforded the following results: Specific gravity (25° C.) = 0.9694; n_D at 20° C. = 1.4780; α_D at 20° C. = −0.35°; solubility in 70 per cent alcohol = 1 : 3; acid number = 0, ester number = 5.0.

On fractionating at 8 mm about 15 per cent of a hydrocarbon was separated. After distilling this over sodium a pleasant smelling liquid was obtained having a boiling point of 176° C. (766 mm); a

specific gravity of 0.8513 at 20° C.; n_D at 20° C., 1.4828; and α_D at 20° C., −18.5°. Cymene was identified in this fraction.

Dextro camphor was identified in the fractions coming over before the ascaridol by means of its semicarbazone and its oxim. The proportion of camphor in the sample was estimated to be at least 4 per cent. This was determined by treating a weighed sample of the oil with semicarbazid hydrochlorid and sodium acetate in acetic acid solution, allowing the mixture to stand for some time, and distilling the oil, after freeing from acetic acid, with steam. As camphor semicarbazone is scarcely volatile with steam, it remained behind in a crude form. This was dried on a porous plate and from its weight the amount of camphor was roughly estimated.

The presence of dextro camphor no doubt accounts for the low lævo rotation of this sample. Camphor was not found in the fresh authentic specimens, and the question therefore arises whether the camphor may be formed in the oil on aging. This question is to be investigated by an examination of the samples in which no camphor was found after aging a year under varying conditions.

The substance which Schimmel & Co. have designated ascaridol was separated as completely as possible by fractionation at 8 mm. Thus purified, it has a constant boiling point, and probably constitutes at least 70 per cent of the sample.

Boiling point, 8 mm = 96° to 97° C.; specific gravity $\left(\frac{20° \text{ C.}}{20° \text{ C.}}\right)$ = 0.9985; n_D at 20° C. = 1.4769; α_D at 20° C. = +0.7°.

Schimmel & Co. found ascaridol to be inactive. The slight optical activity of the ascaridol obtained from this sample is no doubt due to the rather large amount of camphor present from which the ascaridol was not entirely freed on fractionation.

EXPERIMENTS TO DETERMINE THE NATURE OF ASCARIDOL.

The following experiments illustrate the instability of ascaridol: On pouring ascaridol onto mercury, heated to 260° C., it inflames. It is decomposed with explosive violence on adding sulphuric, hydrochloric, nitric, or phosphoric acids, and on warming gently, zinc chlorid. When heated to 140° C., with phthalic anhydrid, it is violently decomposed. No phthalic acid ester was found in the reaction product. When heated to near its boiling point, ascaridol decomposes with explosive violence. If dropped into sulphuric acid a combustible saturated gas is evolved. Treated with acetic anhydrid in pyridin solution, it does not react, either at the temperature of the steam bath or at the boiling point of pyridin. On boiling with acetic anhydrid, however, some ester is apparently formed, but involving a decomposition of the original material. It affords no oxim, no semicarbazone. Phenyl isocyanate does not react.

On shaking ascaridol with a saturated solution of ferrous sulphate, the temperature rises, a combustible gas is evolved, and basic ferric sulphate is precipitated. This reaction indicates that ascaridol may be an unstable oxid. As the reaction with ferrous sulphate appears to go smoothly and is capable of control, its study seemed to promise some light on the chemical nature of ascaridol, and the following experiments were made:

Experiment I.—Fifty cubic centimeters of ascaridol were shaken with saturated solution of ferrous sulphate. The mixture became quite hot, and a small amount of gas was evolved which was collected and found to be combustible. Much basic ferric sulphate was precipitated, and the ascaridol first became colorless and finally quite viscous. Thirty-five cubic centimeters of thick oil were drawn off and the filtered, aqueous solution was extracted with ether. On evaporating the ether a viscous, odorless, water-soluble substance remained, which had a burning taste. Accordingly, the thick oil drawn off at first was shaken out with water, the aqueous extract was shaken out with ether, and an additional quantity of the water-soluble substance obtained.

Experiment II.—Ascaridol, 20 cc, was shaken with ferrous sulphate solution and the entire mixture distilled with steam. The distillate was saturated with sodium chlorid and extracted with petroleum ether, the aqueous solution being then distilled into a 50 cc flask.

The specific gravity $\left(\frac{15.6^\circ\ \text{C.}}{15.6^\circ\ \text{C.}}\right)$ of distillate is 0.9978, equivalent to 0.57 gram (as ethyl alcohol) or 2.85 per cent of the ascaridol. The distillate was then fractionated and the concentrated alcohol examined. It gave iodoform in the cold, and on oxidizing with chromic acid afforded acetone, which was identified by means of its condensation product with benzaldehyde, di-benzylidene acetone, melting point, 111° to 112° C. Therefore, isopropyl alcohol is among the products formed from ascaridol on treatment with ferrous sulphate; 2 cc of oil came over with the steam, the greater part being nonvolatile. This was extracted from the retort residue by means of ether and amounted to 15 cc of a thick, sirupy oil. On acetylation this was found to be alcoholic in nature. The acetyl ester had a decided pennyroyal or pulegone odor, especially upon warming.

Experiment III.—Treated 20 cc of ascaridol with ferrous sulphate solution as before, but kept the temperature down by occasional cooling under the tap. Little, if any, gas was evolved and less basic ferric salt was precipitated than in the previous experiments. The ascaridol, as before, became first colorless, then viscous, and part of it went into solution. In all cases the chenopodium odor almost entirely

disappeared, and the viscous, soluble substance seemed to be the chief product of the reaction.

Experiment IV.—In order to study further this conversion product of ascaridol, a large amount of the latter was prepared from authentic samples of the oil.

Three hundred cubic centimeters of ascaridol were shaken violently with a nearly saturated solution of 100 grams of ferrous sulphate, keeping the temperature below 35° C. by occasional cooling. When the temperature ceased to rise and the mixture had become quite viscous, the reaction was considered at an end. The reaction product was recovered from the mixture by means of ether. On shaking it with benzoyl chlorid and sodium hydrate solution (Schotten-Baumann method), a solid crystalline ester was separated. This was filtered off and dried on a porous plate. Recrystallized from alcohol it melted at from 136° to 137° C. From this ester the pure alcohol was obtained as an odorless, colorless, viscous oil, which crystallizes on long standing in a vacuum desiccator, the crystals rotating like camphor when dropped on water. The alcohol possesses the following physical characteristics: Boiling point, 271° to 272° C.; melting point, 62.5° to 64.0° C.; specific gravity $\left(\frac{20°\text{ C.}}{20°\text{ C.}}\right)$, 1.0981; n_D at 20° C. = 1.4796; $\alpha_D = 0$; molecular refraction, 48.63 (calculated for a saturated compound with two hydroxyls = 48.65). On analysis the formula was found to be $C_{10}H_{18}O_3$.

Chemical data on which the formula of the alcohol was based.

(1) 0.2771 gram gave 0.6522 gram CO_2=0.17787 gram C, and 0.2414 gram H_2O= 0.02704 gram H.

(2) 0.3303 gram gave 0.7776 gram CO_2=0.21207 gram C, and 0.2850 gram H_2O= 0.0319 gram H.

Determinations.	Found.		Calculated for $C_{10}H_{18}O_3$.
	1	2	
	Per cent.	*Per cent.*	*Per cent.*
Carbon	64.19	64.20	64.46
Hydrogen	9.76	9.66	9.74
Oxygen	26.05	26.14	25.80

This alcohol, as will be shown, contains two hydroxyl groups, and therefore is designated as ascaridol glycol.

ASCARIDOL GLYCOL MONO-BENZOATE.

The product of the Schotten-Baumann reaction proved to be a mono-benzoate.

Analysis of the mono-benzoate.

(1) 0.2337 gram gave 0.6052 gram CO_2=0.16505 gram C, and 0.1506 gram H_2O= 0.01673 gram H.

(2) 0.3073 gram gave 0.7888 gram CO_2=0.2151 gram C, and 0.2077 gram H_2O= 0.02308 gram H.

Determinations.	Found.		Calculated for $C_6H_5COC_{10}H_{17}O_3$.
	1	2	
	Per cent.	*Per cent.*	*Per cent.*
Carbon	70.62	70.00	70.34
Hydrogen	7.16	7.51	7.58
Oxygen	22.22	22.49	22.06

0.5183 gram required 3.6 cc of half-normal potassium hydroxid to saponify = 36.46 per cent of C_6H_5CO; calculated for $C_6H_5COC_{10}H_{17}O_3$= 36.21 per cent C_6H_5CO. Crystallizes from warm alcohol in prisms; melting point = 136° to 137° C.

ASCARIDOL GLYCOL DI-BENZOATE.

The second hydroxyl group in ascaridol glycol was shown by the preparation of the di-benzoate. This is formed when the glycol is heated with benzoic anhydrid to 150° C. for two hours. The ester recovered was purified by recrystallizing from alcohol, yielding white, glistening needles. Melting point, 116.5° to 117.5° C.

Analysis of the di-benzoate.

0.1800 gram gave 0.4793 gram CO_2=0.13072 gram C, and 0.1089 gram H_2O=0.10219 gram H.

Determinations.	Found.	Calculated for $(C_6H_5CO)_2C_{10}H_{16}O_3$.
	Per cent.	*Per cent.*
Carbon	72.62	73.05
Hydrogen	6.77	6.64
Oxygen	20.61	20.31

One gram = 10.21 cc half normal potassium hydroxid = 53.62 per cent C_6H_5CO; calculated for $(C_6H_5CO)_2C_{10}H_{16}O_3$ = 53.28 C_6H_5CO.

The glycol was recovered from this di-benzoate by saponification with potassium hydroxid unchanged by the conditions of reaction. The boiling and melting points of the recovered glycol were the same as of that prepared through the mono-benzoate. A peculiarity of the hydroxyls of ascaridol glycol is shown by the fact that only one reacts under the conditions of the Schotten-Baumann method while both react on heating to 150° C. with benzoic anhydrid.

THE RELATION OF GLYCOL TO ASCARIDOL.

Ascaridol glycol does not react with reagents which would characterize it as a ketone or aldehyde, nor does it afford a methoxyl number on subjecting it to the Zeisel method. The third oxygen is therefore, in all probability, an oxid oxygen. In that case ascaridol glycol is quite analogous to pinol glycol, and is the product of hydrating a dioxid. In case ascaridol did not suffer a molecular rearrangement on treatment with ferrous sulphate, or if the reagent merely acted catalytically, resulting in simple hydration, the conclusion would be reached that ascaridol is a glycol anhydrid. In such a case it would seem that hydration should result on treatment with very dilute sulphuric acid, or with ferric salts. Both were tried and were found to produce no glycol whatever. As this seemed to indicate that a molecular rearrangement must take place when ascaridol is treated with solutions of ferrous sulphate, attention was then directed to the product of conversion described by Schimmel & Co., which they obtained on heating ascaridol to 150° C. and which they found to have the same composition as that of the original material. This product was prepared and was found to be the anhydrid of the same glycol obtained by the action of ferrous sulphate on ascaridol, for, on treatment with 2 per cent sulphuric acid, it took up water, with rise in temperature, and the hydrate thus formed gave a plentiful yield of the mono-benzoate with a melting point of from 136° to 137° C. when subjected to the Schotten-Baumann reaction. On heating this mono-benzoate at 150° C. with benzoic anhydrid the di-benzoate (melting point, 116.5° to 117.5° C.) was obtained.

The method of preparing the conversion product is as follows:

Cymene, 15 cc, was heated in a glycerin bath to 150° C. and the ascaridol added in 5 cc portions, not allowing the temperature to rise above 165° C. until 25 cc had been added. The mixture was cooled and hydrated by shaking with 100 cc of 2 per cent sulphuric acid. To the solution 100 cc of 20 per cent sodium hydroxid were added, then 35 cc of benzoyl chlorid. The mixture was shaken until the odor of benzoyl chlorid had disappeared, when it was allowed to stand in the refrigerator overnight. Seventeen grams of the mono-benzoate were recovered, a yield of 40 per cent. It is probable this yield can be increased by altering the method given.

Therefore, ascaridol suffers a molecular rearrangement with the formation of a glycol anhydrid, one oxygen apparently remaining combined with two carbons, as an oxid. By fusion with potassium hydrate or by boiling with a small amount of sodium, ascaridol glycol is changed, in part, into a substance which oxidizes to a greenish-violet color in the air. On acidifying the product from such treatment, adding ferric chlorid and distilling with steam a yellow solu-

tion comes over which gives up its color to ether. On shaking the ether with potassium-hydroxid solution the latter is colored a beautiful violet. This alkaline solution was acidified, extracted with ether, and on evaporation of the solvent, orange-yellow crystals were obtained (melting point, 164°–166° C.). These crystals afford a purple-red color with concentrated sulphuric acid. The anilin derivative was prepared and crystallized in violet-black needles. This substance therefore is evidently αoxythymoquinone, but the amount recovered was very small.

OXIDATION OF ASCARIDOL GLYCOL.

When ascaridol glycol is oxidized with a neutral solution of potassium permanganate, a difficultly soluble crystalline acid is formed in preponderating amount. This separates at once in acidifying the concentrated solution filtered from manganese dioxid. The acid is quite soluble in hot water, but is difficultly soluble in cold water. It crystallizes from water in fine glistening needles; melting point, 116.5° to 117° C.; $\alpha_D = 0$ (2 per cent alcoholic solution).

The formula indicated by analysis is $C_{10}H_{16}O_5$. It is, therefore, isomeric with cineolic acid.

Analysis of the principal acid formed by oxidation of the glycol.

(1) 0.1318 gram gave 0.2681 gram CO_2=0.07312 gram C; 0.0873 gram H_2O=0.0098 gram H.

(2) 0.1429 gram gave 0.2897 gram CO_2=0.0790 gram C; 0.0978 gram H_2O=0.0109 gram H.

Determination.	Found.		Calculated for $C_{10}H_{16}O_5$.
	1	2	
	Per cent.	*Per cent.*	*Per cent.*
Carbon	55.48	55.28	55.52
Hydrogen	7.43	7.62	7.46
Oxygen	37.09	37.10	37.02

This acid, which is the chief oxidation product, will be designated ascaridic acid. It is dibasic. The silver salt, prepared by precipitation, is almost insoluble in water; 0.0637 gram silver salt gave 0.0317 gram Ag = 49.76 per cent; calculated for $C_{10}H_{14}O_5Ag_2$ = 50.00 per cent Ag.

Ascaridic acid reacts neither with hydroxylamin nor with semicarbazid, and is evidently, therefore, not a ketonic acid. After boiling with acetic anhydrid and rehydrating by boiling with water, the acid was recovered unchanged, which would not have been the case had it contained a hydroxyl group. That it is not a lactone or anhydrid is shown by its behavior on titration.

When heated above its melting point, a lighter boiling substance is formed, which has an odor suggestive of amyl acetate. Methyl heptenone is, therefore, probably formed, but sufficient material is not available at present to positively identify it by the preparation of derivatives. This acid is probably closely related to cineolic acid, which breaks down into methyl heptenone on dry distillation.

After separating the ascaridic acid, the solution was distilled with steam, and a small amount of a mixture of volatile acids recovered. These have not been separated, but apparently acetic and butyric acids are present.

The residue, freed from most of the volatile acid, on cooling, deposited crystalline crusts. This was recrystallized from water and proved to be another acid. It is soluble in hot water, but difficultly soluble in cold water. The crystals are brilliant rhombohedra, melting at 186° to 187° C. (with decomposition).

Analysis of acid formed as a minor oxidation product of the glycol.

0.1407 gram gave 0.07175 gram C=51.00 per cent; 0.0100 gram H=7.11 per cent.

Determination.	Found.	Calculated for $C_{10}H_{16}O_6$.
	Per cent.	*Per cent.*
Carbon	51.00	51.69
Hydrogen	7.11	6.95
Oxygen	41.89	41.36

As 0.2066 gram = 17.6 cc tenth normal potassium hydroxid, the neutralizing equivalent is 117.3.

The silver salt was prepared by precipitation; 0.3084 gram gave 0.1486 gram Ag = 48.18 per cent; calculated for $C_{10}H_{14}O_6$, Ag_2 = 48.20 per cent Ag. The acid, therefore, is dibasic, and its formula is evidently $C_{10}H_{16}O_6$. On heating above its melting point, no odor of methyl-heptenone was observed. The amount of these acids available was too small for further examination. Their study is, therefore, reserved for a future communication.

THE CHEMICAL NATURE OF ASCARIDOL.

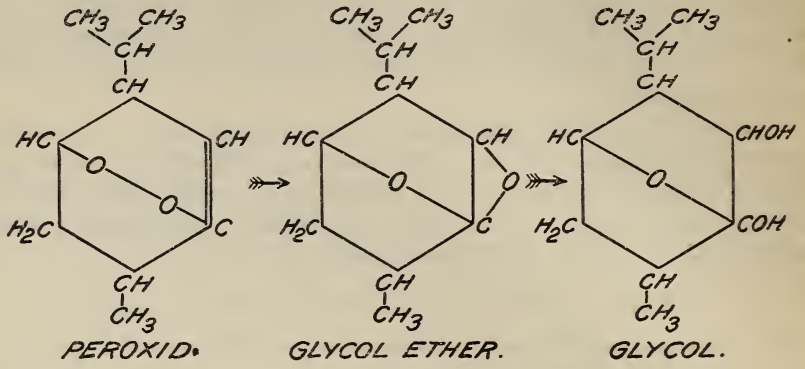
The indifference of ascaridol toward reagents, which would characterize it as an aldehyde, ketone, phenol, or alcohol, taken with the fact that it rearranges to form a glycol anhydrid, analogous to pinol oxid, seems to warrant the conclusion that it is an unstable dioxid.

Its property of exploding when heated and of giving off a combustible gas under certain conditions (which was also observed by Freer [1] in his work on acetyl-benzoyl peroxid), as well as the violence of the

[1] Amer. Chem. J., 1902, 27: 161.

reaction brought about when treated with ferrous sulphate and other reducing agents, seem to indicate that ascaridol is an organic peroxid.

If so, the following tentative structural formulas, which are intended to show a relationship to oxythymo quinone, will indicate the course of the reactions involved:



Approved:

JAMES WILSON,
Secretary of Agriculture.

WASHINGTON, D. C., *April 25, 1911.*

UNIVERSITY OF FLORIDA
3 1262 08929 2741